REMARKS

Claims 1-66 are pending after entry of this Amendment. Claims 67 and 73 have been canceled without prejudice. Claims 4, 9, 29, and 46-48 have been amended. These amendments do not include new matter, as set forth in the following section.

Support in the Specification

Claim 4 has been amended simply to correct a grammatical error, and the amendment does not alter the scope of this claim.

Claim 9 has been amended to place the Markush group in proper alternative form, and this amendment does not alter the scope of this claim.

Claim 29 has been amended simply to correct a grammatical error, and the amendment does not alter the scope of this claim.

Claims 46-48 have been amended simply to clarify that the IR1-promoting agent to which the autologous leukocytes recited in those claims are contacted can, but need not be, IFN-g or the "second IR1-promoting agent" recited in claim 1, from which each of these claims depends. This recitation is supported in the specification, for example at page 20, line 3, through page 21, line 2. These amendments do not alter the scope of these claims.

For the foregoing reasons, the Applicant respectfully contends that the amended claims do not include new matter.

Response to Claim Rejection

The Applicant appreciates the Examiner's observation (Office Action, page 3, third paragraph, third sentence) that the prior art reviewed by the Examiner does not disclose the tumor alleviation methods recited in the claims.

Claims 1-66 stand rejected pursuant to 35 U.S.C. § 112, first paragraph. In the Examiner's view, the specification does not enable one skilled in the art to make and/or use the invention recited in the claims.

The Applicant believes that the Examiner's enablement-type rejection is not proper, because the Examiner does not appear to allege that the specification fails to teach the skilled artisan how to make and use the claimed methods. Instead, the Examiner's rejection

appears to be premised on disbelief by the Examiner that the claimed methods will have the effect disclosed in the specification (i.e., that the methods do not have their disclosed utility). For this reason, the Applicant briefly disposes of the Examiner's enablement rejection in the following section, and responds to the Examiner's apparent concerns regarding utility in the ensuing section.

Enablement Concerns

The methods recited in the claims comprise several steps. All of the pending claims recite (or depend from a claim that recites):

A. locally administering an antigen-releasing agent to a tumor;

B. locally administering a leukocyte attractant to the tumor; and

C. locally administering IFN-g and a second IR1-promoting agent to the tumor.

IFN-g is a known compound, and the specification describes a variety of antigen-releasing agents (e.g., at page 4, lines 27-29), leukocyte attractants (e.g., at page 15, line 25, through page 16, line1), and IR1-promoting agents (e.g., at page 10, lines 22-26). The Examiner has not alleged that the specification fails to teach the identities of these compounds, and the Applicant contends that the skilled artisan is able to identify and select these compounds based on the disclosure in the specification and what was known in the art as of the filing date.

The specification also describes (e.g., at page 13, lines 13-15) numerous methods of locally administering agents to tumors. The Examiner has not alleged that the specification fails to teach how to locally administer agents to a tumor, and the Applicant contends that the skilled artisan is able to do so based on the disclosure in the specification and what was known in the art as of the filing date.

The Applicant respectfully contends that the specification discloses enough information that the skilled artisan is enabled to perform the methods (i.e., including A, B, and C above) recited in the claims.

Some claims (e.g., 37-43 and 66) recite

D. locally administering a type 1 lymphocyte attractant to the tumor.

The specification describes numerous such attractants (e.g., at page 5, line 7). The Examiner has not alleged that the specification fails to teach the identities of lymphocyte attractants, and the Applicant contends that the skilled artisan is able to identify and select these attractants based on the disclosure in the specification and what was known in the art as of the filing date. The Applicant therefore respectfully contends that the specification discloses enough information that the skilled artisan is enabled to perform the claimed methods that include item *D*.

Some claims (e.g., 40, 44-51, and 66) recite

E. locally administering autologous lymphocytes to the tumor.

The specification describes numerous methods of obtaining, expanding, and locally administering autologous lymphocytes (e.g., at page 19, line 9, through page 21, line 2). The Examiner has not alleged that the specification fails to teach these methods, and the Applicant contends that the skilled artisan is enabled to isolate, expand, and administer autologous lymphocytes based on the disclosure in the specification and what was known in the art as of the filing date. The Applicant therefore respectfully contends that the specification discloses enough information that the skilled artisan is enabled to perform the claimed methods that include item *E*.

Some claims (e.g., 41, 42, 52, and 66) recite

F. administering a memory cell-inducing agent to the patient.

The specification describes numerous such agents (e.g., at page 21, lines 17-20). The Examiner has not alleged that the specification fails to teach the identities of memory cell-inducing agents, and the Applicant contends that the skilled artisan is able to identify and select these agents based on the disclosure in the specification and what was known in the art as of the filing date. The Applicant therefore respectfully contends that the specification discloses enough information that the skilled artisan is enabled to perform the claimed methods that include item *F*.

Some claims (e.g., 42, 43, 50, 51, and 57-66) recite

G. supplementing the patient's nutrition.

Nutritional supplementation is well known in the art, and the specification also describes preferred methods of supplementation (e.g., at page 22, lines 6-22). The Examiner has not alleged that the specification fails to sufficiently teach nutritional supplementation, and the Applicant contends that the skilled artisan is able to supplement a patient's nutrition based on the disclosure in the specification and what was known in the art as of the filing date. The Applicant therefore respectfully contends that the specification discloses enough information that the skilled artisan is enabled to perform the claimed methods that include item G.

In summary, the Applicant respectfully contends that the specification includes sufficient description to enable a skilled artisan to perform every action recited in the claimed methods. The Applicant therefore contends that the claims are fully enabled. Reconsideration and withdrawal of the Examiner's rejection of claims 1-66 pursuant to 35 U.S.C. § 112, first paragraph, are respectfully requested.

Utility Concerns

The Applicant believes that the Examiner's enablement concern stems from the Examiner's apparent belief that the claimed methods cannot be used to alleviate a tumor (i.e., that the specification does not adequately teach how to use the claimed methods). This appearance is created by the Examiner's statements in the Office Action (page 3, third paragraph) that anti-tumor effects of individual steps recited in the claims was not described in the prior art, that the specification does not exemplify alleviation of a tumor, and that "it would have been unpredictable to practice the invention as claimed" (Office Action, page 4, final sentence of first partial paragraph). As described in the preceding section entitled "Enablement," the Applicant believes that the specification teaches how to perform each and every step of the claimed methods, and that at least the "how to make" portion of the enablement requirement is met. The Applicant believes that demonstrating that the claimed methods exhibit a patentable utility (i.e., in combination with the demonstration above that the specification adequately teaches how to

perform those methods) will cause the Examiner to conclude that the specification also satisfies the "how to use" portion of the enablement requirement.

An invention claimed in a patent application has a patentable utility if that utility is either i) a well-established utility or ii) a specific, substantial, and credible utility asserted in the specification by the Applicant. The invention here (i.e., 'what is claimed') is a method of alleviating a tumor, the method comprising locally administering 1) an antigen-releasing agent, 2) a leukocyte attractant, 3) IFN-g, and 4) a second IR1-promoting agent to the tumor. The Applicant does not dispute that it is not well-established in the art that local administration of these four agents to a tumor will alleviate the tumor. However, the Applicant believes that the assertion in the specification that these four steps can be used to achieve this purpose represents a specific, substantial, and credible utility.

The Examiner does not appear to dispute that alleviation of a tumor represents a substantial utility, and the Applicant believes that no reasonable argument can be made to the contrary. The Applicant therefore assumes that the asserted utility is substantial.

A specific utility is one that is specific to the subject matter claimed (i.e., not a 'general' utility applicable to most or substantially all subject matter of the same type as that claimed; see MPEP § 2107.01). Here, the Applicant does not assert a utility that would be shared by many or most combinations of compounds that could potentially be locally administered to a tumor. Instead, the utility that is asserted is specific to the particular combinations of compounds recited in the claims. The Applicant therefore contends that the asserted utility is specific to the subject matter claimed.

The Examiner's comments relating to the alleged unpredictability of using the claimed methods suggests to the Applicant that the Examiner questions the credibility of the asserted utility. As a preliminary matter, the Examiner is reminded that a utility asserted in a patent application is presumed to credible, and that the Examiner **MUST** accept the credibility of the asserted utility **UNLESS** there is reason for one skilled in the art to question the objective truth of the asserted utility or its scope. That is, the Examiner has the burden to "do more than merely question operability - [she] must set forth factual reasons which would lead one skilled in the art to question the objective truth of the statement of operability" *In re Gaubert* 524 F. 2d 1222, 1224, 187 USPQ 664, 666 (CCPA, 1975). "An assertion is credible unless (A) the logic

underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion" MPEP § 2170.02(III)(B). The Applicant was careful to explain the logic underlying the asserted utility of the claimed methods in the specification. That logic is summarized below.

Each of the pending claims recites (or depends from a claim that recites) local administration of four agents to a tumor. The four agents are 1) an antigen-releasing agent, 2) a leukocyte attractant, 3) IFN-g, **AND** 4) a second IR1-promoting agent. The logic relating to these agents is discussed separately in the ensuing four paragraphs.

1) Antigen-Releasing Agent

As discussed in the specification at page 10, lines 9-17, local administration of the antigen-releasing agent induces release of antigens from tumor cells and induces immune responses which are specific for tumor cells. This response is known in the art, as evidenced, for example, by the Gallucci et al. reference (2001, Curr. Op. Immunol. 13:114-119) listed in the IDS, which summarizes the knowledge in the field at about the time the application was filed, with regard to release of factors by damaged tissues. Release of antigens from tumor cells provides a substrate which can be acted upon by leukocytes attracted to the tumor site in order to render the resulting immune response specific for tumor cells. Release of antigens from tumor cells also establishes a gradient of antigen which can 'direct' activated immune cells to the tumor site.

2) Leukocyte Attractant

As discussed in the specification at page 10, lines 18-21, and at page 15, lines 22-29, local administration of one or more leukocyte attractants induces recruitment of leukocytes to the tumor site. It is well known that leukocytes are involved in mobilization of an immune response. Attraction of leukocytes using various agents (e.g., chemokines) is disclosed, for example, in the Mantovani reference (1999, Immunol. Today 20:254-257) listed in the IDS. The relevance of leukocytes attracted to the site becomes apparent below.

3) and 4) IFN-g and a Second IR1-Promoting Agent

As discussed in the specification at page 10, line 22, through page 11, line 9, and at page 18, lines 5-12, local administration of these agents induces leukocytes at the tumor site to exhibit a type 1 inflammatory response. Part of the type 1 inflammatory response is a cytotoxic

response. Thus, leukocytes that are attracted to the tumor site interact with antigens released from tumor tissue and are induced (i.e., by the IR1-promoting agents) to mount a cytotoxic response against tumor cells, thereby killing some or all of the tumor cells and alleviating the tumor.

The Applicant respectfully contends that the specification discloses a logical explanation of how the claimed methods operate (even though, of course, patentability is not dependent on the accuracy of this explanation). The Examiner has not cited any logical flaw in the explanation offered in the specification, nor has she cited facts that are inconsistent with the logic of this explanation. The Applicant respectfully contends that a skilled artisan reading the specification would not have any legitimate basis to doubt the credibility of the explanation in the specification. For this reason, the Examiner has not met the burden of demonstrating that the utility asserted for the claimed methods is incredible.

Other, optional steps that are disclosed in the specification include

- locally administering a type 1 lymphocyte attractant to the tumor site (i.e., in order to recruit additional leukocytes that already exhibit a type 1 inflammatory response to the site, as described in the specification at page 19, lines 12-22),
- providing expanded, differentiated, or expanded and differentiated leukocytes to the tumor site (i.e., in order to recruit additional leukocytes to the site, whether they already exhibit the type 1 inflammatory response or are induced to exhibit this response by the IR1-promoting agents at the site, as described in the specification at page 19, line 23, through page 21, line 2),
- administering a memory cell-inducing agent to the patient (i.e., in order to inhibit or prevent recurrence of the tumor, as described in the specification at page 21, lines 13-20), and
- supplementing the patient's nutrition (i.e., in order to enhance immune function, as described in the specification at page 22, lines 7-22).

The Applicant respectfully contends that none of these other, optional steps lacks a credible basis from which a skilled artisan would expect improvement of the basic method described above. Neither has the Examiner cited logical flaws or inconsistent facts that would contradict the explanation in the specification for the usefulness of each of these other, optional steps.

Therefore, the Examiner has not met her burden of demonstrating that the asserted utility is incredible.

For the foregoing reasons, the Applicant respectfully contends that the specification asserts a specific, substantial, and credible utility (i.e., a patentable utitlity) for the claimed methods. As described in the section of this Amendment entitled "Enablement," the specification sufficiently describes to a skilled artisan how to perform each of the steps recited in the claimed methods. For these reasons, the Applicant respectfully contends that the specification satisfies both the "how to make" and "how to use" portions of the enablement requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the Examiner's rejection of claim 1-66 on that basis are respectfully requested.

Summary

The Applicant respectfully submits that every rejection of the pending claims has been overcome or is now inapplicable, and that each of claims 66 is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date. If the Examiner believes that a telephone interview would expedite allowance of the claims, then the Examiner is requested to contact the undersigned representative.

Respectfully submitted,

Eugene Roussel

10 April 2002 By: _____

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Enclosures: Petition for Extension of Time
Marked-Up Copy of Claims Amended
Clean Copy of Claims as Amended

Marked-Up Copy of Claims Amended in the Amendment Responding to the Office Action Dated 10 December 2001

4. (Amended) The method of claim 3, wherein the antigen-releasing agent comprises a proteolytic enzyme ~~is~~ selected from the group consisting of trypsin, chymotrypsin, pepsin, and collagenase.

9. (Amended) The method of claim 7, wherein the alkylphosphocholine is selected from the group consisting of hexadecylphosphocholine ~~or~~ and edelfosine.

29. (Amended) The method of claim 1, wherein the second IR1-promoting agent is selected from the group consisting of interleukin-2 (IL-2), interleukin-12 (IL-12), tumor necrosis factor-alpha (TNF-a), and tumor necrosis factor-beta (TNF-b).

46. (Amended) The method of claim 44, wherein the autologous leukocytes are obtained from the patient and contacted with an independently-selected IR1-promoting agent prior to locally administering them to the tumor.

47. (Amended) The method of claim 44, wherein the autologous leukocytes are obtained from the patient, expanded ex vivo, and contacted with an independently-selected IR1-promoting agent prior to locally administering them to the tumor.

48. (Amended) The method of claim 47, wherein the leukocytes are contacted with both ~~an~~ the independently-selected IR1-promoting agent and with at least one of interferon-alpha (IFN-a) and IL-12 prior to locally administering them to the tumor.